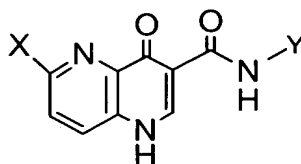


Claims

What is claimed is:

1. A pharmaceutical composition comprising an acetylcholinesterase inhibitor and an inverse agonist of the GABA_A α 1 and/or α 5 receptor subtype wherein the inverse agonist has a functional efficacy at the α 1 and/or α 5 receptor subtypes of less than -5%, preferably less than -10%, and the efficacy measured at the α 2 and α 3 receptor subtypes is greater than 5% or preferably greater than 10%, and a pharmaceutically acceptable carrier, said composition being effective in the treatment of a cognitive disorder.
2. The pharmaceutical composition of claim 1, wherein the inverse agonist has a functional potency (EC₅₀ values) at the α 1 and/or α 5 receptor subtypes of 200 nM, preferably less than 150 nM.
3. The pharmaceutical composition of claim 1, wherein the inverse agonist has a functional efficacy at the α 5 receptor subtype of less than -5%, preferably less than -10%, and the efficacy measured at the α 1, α 2 and α 3 receptor subtypes is greater than 5% or preferably greater than 10%.
4. The pharmaceutical composition of claim 3, wherein the inverse agonist has a functional potency (EC₅₀ values) at the α 5 receptor subtype of 200 nM, preferably less than 150 nM.
5. The pharmaceutical composition of claim 1, wherein the inverse agonist at the α 1 and/or α 5 receptor subtypes has a binding K_i of 100 nM, preferably less than 30 nM.
6. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, a GABA_A inverse agonist, and an acetylcholinesterase inhibitor, wherein said GABA_A inverse agonist is selected from a compound of Formula I below:



I

wherein:

X is hydrogen, halogen, $-OR_1$, NR_2R_3 , C_1-C_6 alkyl optionally substituted with up to three groups selected independently from halogen and hydroxy, or $-NR_2R_3$; or

X is phenyl, naphthyl, 1-(5,6,7,8-tetrahydro)naphthyl or 4-(1,2-dihydro)indenyl, pyridinyl, pyrimidyl, isoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, benzofuranyl, benzothieryl, each of which is optionally substituted with up to three groups selected from halogen, C_1-C_6 alkyl, C_1-C_4 alkoxy, C_1-C_6 alkylthio, hydroxy, amino, mono or di(C_1-C_6) alkylamino, cyano, nitro, trifluoromethyl; or

X represents a carbocyclic group ("the X carbocyclic group") containing from 3 - 7 members, up to two of which members are optionally hetero atoms selected from oxygen and nitrogen, where the X carbocyclic group is optionally substituted with one or more groups selected from halogen, (C_1-C_6)alkoxy, mono- or di(C_1-C_6)alkylamino, sulfonamide, aza(C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkylthio, (C_1-C_6)alkylthio, phenylthio, or a heterocyclic group; and

Y is lower alkyl having 1 - 8 carbon atoms optionally substituted with up to two groups selected from halogen, (C_1-C_6)alkoxy, mono- or di(C_1-C_6)alkylamino, sulfonamide, aza(C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkylthio, (C_1-C_6)alkylthio, phenylthio, a heterocyclic group, $-OR_4$, $-NR_5R_6$, SR_7 , or aryl; or

Y is a carbocyclic group ("the Y carbocyclic group") having from 3 - 7 members atoms, where up to three of which members are optionally hetero atoms selected from oxygen and nitrogen and where any member of the Y carbocyclic group is optionally substituted with halogen, $-OR_4$, $-NR_5R_6$, SR_7 , aryl or a heterocyclic group; and

R_1 is hydrogen, lower alkyl having 1 - 6 carbon atoms, or cycloalkyl having 3 - 7 carbon atoms, where each alkyl may be optionally substituted with $-OR_4$ or $-NR_5R_6$;

R_2 and R_3 are the same or different and represent hydrogen, lower alkyl optionally mono- or disubstituted with alkyl, aryl, halogen, or mono- or di-lower alkyl;

aryl or aryl (C₁-C₆)alkyl where each aryl is optionally substituted with up to three groups selected from halogen, hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, or mono- or di (C₁-C₆)alkylamino;

5 cycloalkyl having 3 – 7 carbon atoms optionally mono or disubstituted with halogen, alkoxy, or mono- or di- lower alkyl; or

-SO₂R₈;

R₄ is as defined for R₁;

R₅ and R₆ carry the same definitions as R₂ and R₃, respectively;

10 R₇ is hydrogen, lower alkyl having 1 – 6 carbon atoms, or cycloalkyl having 3 – 7 atoms; and

R₈ is lower alkyl having 1 – 6 carbon atoms, cycloalkyl having 3 – 7 carbon atoms, or optionally substituted phenyl,

or a pharmaceutically acceptable prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug,

15 said composition being effective in the treatment of a cognitive disorder.

7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, a GABA_A inverse agonist, and an acetylcholinesterase inhibitor, wherein the GABA_A inverse agonist is selected from the group consisting of:

20 N-n-Butyl-6-chloro-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-n-Butyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(2-Ethylthio)ethyl-6-methoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-n-Pentyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

25 N-Benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(2-Tetrahydrofuranyl)methyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-Isoamyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

30 N-(3-Methoxybenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(3-Ethoxy)propyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-2-(2-Methyl)butyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-

carboxamide;

N-5-Pentanol-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-

carboxamide;

N-Benzyl-6-methoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

5

N-(2-Fluorobenzyl)-6-methoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-

carboxamide;

N-(3-Fluorobenzyl)-6-methoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-

carboxamide;

N-(4-Fluorobenzyl)-6-methoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-

10

carboxamide;

N-(4/5-Imidazolyl)methyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(3-Thienyl)methyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-

carboxamide;

15

N-(2-Tetrahydropyranyl)methyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(2-Fluorobenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-

carboxamide;

N-(3,5-Fluorobenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-

20

carboxamide;

N-(4-Fluorobenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-

carboxamide;

N-(4-Methoxybenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-

carboxamide;

25

N-(4-Methylbenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-

carboxamide;

N-(2-Thienyl)methyl-6-(2-methoxyethoxy)-4-oxo-1,4-tetrahydro-1,5-

naphthyridine-3-carboxamide;

N-(2-Thienyl)methyl-6-morpholino-4-oxo-1,4-tetrahydro-1,5-naphthyridine-

30

3-carboxamide;

N-(2-Thienyl)methyl-6-dimethylamino-4-oxo-1,4-tetrahydro-1,5-

naphthyridine-3-carboxamide;

N-(4-Methylaminomethyl)benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-

naphthyridine-3-carboxamide;

Sub
A1
cont.

09076347-101204
TOP SECRET

N-(3-Methylaminomethyl)benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide hydrochloride;

N-[4-(Imidazolylmethyl)benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide,

5 a pharmaceutically acceptable prodrug thereof, and a pharmaceutically acceptable salt or solvate of said compound or prodrug,

said composition being effective in the treatment of a cognitive disorder.

8. The pharmaceutical composition of claim 7, wherein the GABA_A inverse agonist is N-Benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide, or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.

9. The pharmaceutical composition of claim 7, wherein the acetylcholinesterase inhibitor is selected from the group consisting of Aricept (donepezil, E2020), Exelon (rivastigmine), metrifonate, galantamine, physostigmine, tacrine, huperzine A, and icopezil, a prodrug thereof, and a pharmaceutically acceptable salt or solvate of said compound or prodrug.

10. The pharmaceutical composition of claim 9, wherein the acetylcholinesterase inhibitor is Aricept (donepezil, E2020) or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.

11. The pharmaceutical composition of claim 7, wherein the GABA_A inverse agonist is N-Benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide, or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug; and the acetylcholinesterase inhibitor is Aricept (donepezil, E2020) or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.

12. A method for treating a cognitive disorder in a mammal, comprising administering to a mammal in need of such treatment an effective amount of a combination of a GABA_A inverse agonist and an acetylcholinesterase inhibitor,

Sub
A
cont.

09976347-10130
FOI 2025-00000

Figure 6. The effect of the number of iterations (n) on the accuracy of the proposed algorithm. The results are shown for different values of α and β . The x-axis represents the number of iterations (n), ranging from 0 to 100. The y-axis represents the error, ranging from 0 to 1. The legend indicates three cases: $\alpha = 0.5, \beta = 0.5$ (blue line with circles), $\alpha = 0.7, \beta = 0.3$ (red line with squares), and $\alpha = 0.9, \beta = 0.1$ (green line with triangles). In all cases, the error decreases as the number of iterations increases, with the rate of decrease being higher for larger values of α .

13. The method of claim 12, wherein the GABA_A inverse agonist is N-Benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide, or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.
14. The method of claim 12, wherein the acetylcholinesterase inhibitor is selected from the group consisting of Aricept (donepezil, E2020), Exelon (rivastigmine), metrifonate, galantamine, physostigmine, tacrine, huperzine A, and icopezil, a prodrug thereof, and a pharmaceutically acceptable salt or solvate of said compound or prodrug.
15. The method of claim 12, wherein the acetylcholinesterase inhibitor is Aricept (donepezil, E2020) or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.
16. The method of claim 12, wherein the GABA_A inverse agonist is N-Benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide, or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug; and the acetylcholinesterase inhibitor is Aricept (donepezil, E2020) or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.
17. The method of claim 12, wherein the GABA_A inverse agonist and the acetylcholinesterase inhibitor are administered separately.
18. The method of claim 12, wherein the GABA_A inverse agonist and the acetylcholinesterase inhibitor are administered sequentially.
19. The method of claim 12, wherein the GABA_A inverse agonist and the acetylcholinesterase inhibitor are administered simultaneously.

Sub
AI
cont

—
